REMARKS

The Examiner provides a number of rejections and we list them here in the order in which they are addressed:

I. Claims 1-40 are rejected under 35 USC §112, ¶1 as allegedly failing to comply with the enablement requirement.

II. Claims 29-40 are rejected under 35 USC §112, ¶1 as allegedly failing to comply with the written description requirement.

III. Claims 2-4, 14-15, 23, 25-26, and 29-40 are rejected under 35 USC §112, ¶2 as allegedly being indefinite and Claims 36-40 are objected to for an alleged improper construction.

IV. The Specification is objected to for allegedly not disclosing a priority statement.

I. Claims 1-40 Are Enabled

The Examiner states that "... the guidance provided by the specification does not correlate to use of any particular saliva specific regulatory element for the creation of transgenic non-human mammals ... *Office Action pg. 8.* The Applicant disagrees and points out that several salivary promoters are discussed and exemplified. For example,

> Among particular preferred control regions in this regards are those of genes of the multi-gene family of proline-rich proteins ("PRP"), in particular the promoters of PRP genes.

Applicant's Specification, pg 17 ln 8-10, and

> The mouse PSP gene has been cloned and characterized by Shaw and Schibler ... The region of 5' flanking DNA required for salivary gland-specific expression is about 4.6 kb; but longer regions, extending further upstream may provide higher levels of expression.

Applicant's Specification, pg 27 11-18, and

> ... genes for rat salivary-gland B1-immunoreactive proteins of adult (and neonatal) rat sublingual and parotid glands (often referred to as the B1-Ips) ... The transcriptional control elements of these genes, and their homologs and paralogs are suitable to engineer salivary gland ... expression of genes ...

Applicant's Specification, pg. 28 ln 15-21. The Examiner, however, has been distracted by the "incorporation by reference" for some non-patent publications mentioned in the Applicant's Specification: "Applicant is reminded that subject matter essential to the claimed invention may not be incorporated by reference to a non-patent publication" *Office Action pg 9.*

A. Incorporated Patents Enable The Claimed Embodiment

In regards to a "germ line" embodiment, which is covered within the scope of the above recited claims, the Examiner asserts that:

> Given the lack of guidance and absence of working examples provided by the specification correlating to creation of transgenic non-human mammals, the lack of guidance provided by the specification with respect to use of saliva regulatory elements, the unpredictability of saliva regulatory elements, it would have required undue experimentation for the skilled artisan to practice the claimed invention.

Office Action pg. 12. The Applicants disagree. The Examiner has, apparently, overlooked the numerous United States Patents that are "incorporated by reference" that properly enable the Applicant's claimed embodiment. These patents provide the necessary technical details to support the Applicant's claimed embodiments and explicitly provide evidence that one skilled artisan would not be faced with undue experimentation to practice the claimed invention.

1. Prothrombin Nucleic Acid Sequence

The Applicant points to the disclosure of Accession No. J00307 in the Applicant's specification (Applicant's Specification at pg 84 ln 20). This sequence, combined with Holly et al., "Methods For Producing Thrombin" *US Pat No; 5,476,777* (Filed: December 30, 1992)(Applicant's Specification at pg 84 ln 27) provides enablement for the Applicant's claimed embodiments:

> The DNA sequence and deduced amino acid sequence of a human prothrombin cDNA sequence is shown in Sequence I.D. Nos. 2 and 3. *col 14 ln 34-38.*

and,

> A prothrombin expression vector was constructed using synthetic oligonucleotides designed to encode the prothrombin leader. Synthetic nucleotides were designed to form, when annealed, an adapter encoding the human prothrombin leader having a 5' Eco RI adhesive end and a 3' Sst I end. Oligonucleotides ZC1378, ZC1379, ZC1323 and ZC 1324 (Sequence ID Nos. 8, 9, 6 and 7, respectively) were kinased and annealed using the method essentially described by Sambrook et al. ... *col 14 ln 39-47.*

2. Transgenic Mammal Creation

The Applicant has enabling support for the production of a transgenic mammal (i.e., for example, a bovine) by using genetic engineering techniques known in the art as presented in Deboer et al., "Production Of Recombinant Polypeptides By Bovine Species And Transgenic Methods" *US Pat No. 6,140,552* (Filed: June 7, 1995)(Applicant's Specification at pg 75 ln 16)[emphasis added]. In addition to presenting technical detail that enables the Applicant's claimed embodiments, Deboer et al. also makes clear that these protocols are considered standard procedures:

> When, the ultimate goal is to secrete a recombinant polypeptide, a "secretory DNA sequence" encoding a functional secretion signal peptide is also operably linked within the transgene to direct secretion of the recombinant polypeptide from one or more cell types within the transgenic animal. ... Secretory DNA sequences from proteins secreted from other cell types within the species of transgenic animal may also be used, e.g., the native signal sequence of a homologous gene encoding a protein secreted other than in the mammary glands. *col 13 ln 23-40.*

and,

> The above described linking of various DNA sequences to form the transgene of the invention are performed by standard methods known to those skilled in the art ... Once the transgene or overlapping homologous fragments encoding the transgene are constructed as described they are used to make transgenic non-human animals. *col. 15 ln 45-51.*

and,

> Methods of introducing transgenes or overlapping transgene fragments into embryonal target cells include microinjection of the transgene into the pronuclei of fertilized oocytes or nuclei of ES cells of the non-human animal. ... In this preferred embodiment, the fertilized oocytes are first microinjected by standard techniques. They are thereafter cultured in vitro until a "pre-implantation embryo" is obtained. ... Such pre-implantation embryos are thereafter transferred to an appropriate female by standard methods to permit the birth of a transgenic or chimeric animal depending upon the stage of development when the transgene is introduced. As is well known, mosaic animals can be bred to form true germline transgenic animals. *col 15 ln 52 – col 16 ln 22.*

The Examiner is further requested to inspect the numerous experiments presented in Doeber et al. that the Applicant has "incorporated by reference" to exemplify their techniques:

EXAMPLE 1: Construction of a Probe Specific for Bovine aS1 Casein Sequences

EXAMPLE 3: Construction of bovine aS1-casein CAT vectors.

EXAMPLE 5: Bovine aS1-casein/hLF expression plasmids.

EXAMPLE 6: In vitro Maturation, Fertilization and Culture of Bovine Oocytes.

EXAMPLE 7: Microinjection of hLF Transgene into Bovine Pronuclei.

EXAMPLE 13: Alternate Construction of Transgenes Encoding hLF.

EXAMPLE 15: Generation of hLF Transgenic Cattle.

Clearly the "incorporation by reference" of Deober et al. provides all the necessary enablement and level of skill in the art supporting the production of any transgenic mammal to express an exogenously incorporated nucleic acid that results in secretion of the encoded polypeptide into the saliva.

Similarly, other techniques to develop transgenic mammals are also disclosed regarding the production of transgenic mice and have been incorporated by reference as described in Krimpenfort et al., "Transgenic Mice Depleted In Mature T-Cells And Methods For Making Transgenic Mice", *US Pat No. 5,175,384* (Filed: Dec. 5, 1988)(Applicant's Specification at pg 38 ln 23-24).

In view of, Deober et al. and Krimpenfort et al., the Applicants respectfully request the Examiner withdraw the rejection.

II. Claim 29-40 Are Adequately Described

The Examiner states that:

> The DNA sequences of all cis-acting expression signals necessary for salivary gland expression and saliva-specific expression of a polypeptide of interest encompassed within the genus of salivary gland and saliva-specific cis-acting expression signals have not been disclosed.

Office Action pg. 5. The Applicant disagrees. Claims 29-40 are rejected under 35 USC 112 as allegedly failing the written description requirement. The Examiner cites numerous cases (e.g. the Eli Lilly case and others) for the proposition that Applicant is not in possession of the genus of saliva specific cis-acting elements. The Examiner's case law is off point. Claims 29-40 are method claims – not composition claims. Applicant is not claiming the genus of saliva specific cis-acting elements. Claims 29-40 merely utilize such elements in the method.

There are many methods patented by the PTO that call out for the use of various elements. These methods are generic, i.e. various different versions of these elements can be substituted. The steps of the method are claimed – not the elements.

Moreover, in most of the cases cited by the Examiner, the novelty was the composition, i.e. the element was not known. By contrast, the present method claims do not require the use of novel cis-acting elements; known saliva specific cis-acting elements are quite satisfactory.

Indeed, there are a number of such known elements – and these are cited in the specification (*infra*).

Moreover, Applicants provide evidence below that the specification does fully describe the invention in accordance with current patent law and judicial interpretation.

A. Incorporated Patents\Publications Establish Knowledge Known In The Art

The Applicant points out that the numerous non-patent literature references are noted with an "incorporation by reference" to incorporate non-essential matter that "establishes the state of the art"[1]. The Examiner has ignored the fact that plasmid construction and transgenic animal production are, in fact, known procedures to those having ordinary skill in the art.

The Examiner is reminded that genetic engineering techniques regarding cloning and transgenic animals are well known to those having skill in the art (i.e., institutional and corporate research scientists) as well as to the general public (i.e., libraries, newspaper articles etc.). The Federal Circuit has clearly stated that an application for patent need not be cluttered with well known information:

> Paragraph 1 permits resort to material outside the specification in order to satisfy the enablement portion of the statute because it makes no sense to encumber the specification of a patent with all the knowledge of the past concerning how to make and use the claimed invention.

Atmel Corp. v. Information Storage Devices, Inc., 198 F.3d 1374, 1382, 53 USPQ2d 1225, 1230 (Fed. Cir. 1999); see also, *Spectra-Physics, Inc. v. Coherent, Inc.* 827 F.2d 1524, 1534, 3 USPQ2d 1737, 1743 (Fed. Cir. 1987), *cert. denied* 484 U.S. 954 (1987)("A patent need not teach, and preferentially omits, what is well known in the art.")[emphasis added]; *Paperless Accounting, Inc., v. Bay Area Rapid Transit Sys.*, 804 F.2d 659, 664, 231 USPQ 649, 653 (Fed. Cir. 1986), *cert denied*, 480 U.S. 933 (1987)("A patent applicant need not include in the specification that which is already known to and available to the public")[emphasis added].

[1] Nonessential subject matter is subject matter referred to for purposes of indicating background of the invention or illustrating the state of the art. *MPEP 608.01(p) Completeness.*

Consequently, a precise recitation of exactly what nucleic acids, vectors, and proteins are used is not required in an application where publications incorporated by reference provide evidence that those in the art consider that techniques working with any nucleic acids, vectors, and proteins are well known. Contrary to the Examiner's opinion, some of the publications below provide evidence that an "operably linked" promoter, if shown for one construct, is expected by those having ordinary skill in the art to work for all constructs.

1. The Salivary Protein Genes

As referred to above, the Applicant has contemplated using a human salivary proline rich protein (PRP) gene and or a parotid secretory protein (PSP) gene to drive expression of an exogenous nucleic acid sequence. Disclosure of both of these genes were in the public domain well before the Applicant filed the instant application and has been admitted by those having ordinary skill in the art to be known.

The amino acid of one PRP protein was first reported in 1983:

> Three basic proline-rich peptides were newly isolated from human parotid saliva, and designated as P-G, P-H, and P-I. The amino acid sequence of P-H was determined to be Ser-Pro-Pro-Gly-Lys-Pro-Gln-Gly-Pro-Pro-Gln-Gln-Glu-Gly-Asn-Asn- Pro-Gln-Gly-Pro-Pro-Pro-Pro-Ala-Gly-Gly-Asn-Pro-Gln-Gln-Pro-Gln-Ala-Pro-Pro-Ala-Gly-Gln-Pro-Gln-Gly-Pro-Pro-Arg-Pro-Pro-Gln-Gly-Gly-Arg-Pro-Ser-Arg-Pro- Pro-Gln by conventional methods.

Saitoh et al., "Further fractionation of basic proline-rich peptides from human parotid saliva and complete amino acid sequence of basic proline-rich peptide P-H" *J Biochem (Tokyo)* 94:1991-1999 (1983). Preliminary nucleic acid sequences for PRP genes were known, and publicly available, in 1984 that identify the regulatory site:

> In Fig. 2B we present ...[a]... consensus sequence for the tandem repeats from PRP1 and PRP2 as a nucleotide sequence and as a decoded sequence of 21 amino acids ... <u>On the 5' side</u> of the tandemly repeated 63-bp elements in both PRP1 and PRP2 the composition of the coding strand of the DNA abruptly becomes very T-rich (bases 1-97), in marked contrast to the 63-bp repeated elements ... These observations suggest that the PRP1 and PRP2 sequences <u>contain an intron upstream</u> of the tandemly repeated proline-rich part of the gene.

Azen et al., "Clones From The Human Gene Complex Coding For Salivary Proline-Rich Proteins" *Proc. Natl. Acad. Sci USA* 81:5561-5565 (1984)[emphasis added]. Quickly, complete PRP nucleic acid sequences became known, and were publicly available, in 1985 that have homologous secretory signal sequences:

> We find that both groups share a homologous 5' untranslated and secretory signal sequence ... [and] ... used a probe made from this region to isolate 19 full length cDNA clones for PRPs. ... They are composed of four domains ... a secretory signal sequence ... N-terminal regions ... [restriction enzyme] repeats ... and the C-terminal region.

Maeda et al., "Differential RNA splicing and post-translational cleavages in the human salivary proline-rich protein gene system" *J Biol Chem* 260:11123-30 (1985).

2. Creation Of Transgenic Animals

The above knowledge regarding salivary protein genes was then developed into the now known techniques to create transgenic animals. Basic genetic engineering protocols to produce transgenic animals, in general, have been established by those having ordinary skill in the art as known. For example:

> The particular composition or form of the exogenous genetic material is not critical. ... Techniques for obtaining DNA sequences by gene excising, splicing, synthesis, isolation, purification and cloning as well as enzymes used in such processes, vehicles and hosts for cloning of recombinant DNA, screening and selection of cloned DNA and detection and analysis of expression of cloned genes are known in the art. *col 7 ln 23-40.*

and,

> The exogenous genetic material is preferentially inserted into the nucleic genetic material by microinjection. Microinjection of cells and cellular structures is known and is used in the art. *col. 8 ln 12-15.*

Wagner et al., "Genetic Transformation Of Zygotes" *US Pat No. 4,873,191* (Filed: August 18, 1986)(incorporated by reference in Applicant's Specification; pg 38 ln 22-23)[emphasis added]. Another skilled in the art states that:

> The production and use of cloned genes, recombinant DNA, vectors, transformed cells ... by genetic engineering are well-known to those skilled in the art. *col 5 ln 20-23.*

Lord S.T., "Method For Recombinant Fibrinogen Production" *US Pat No; 6,037,457* (Filed: January 31, 1997)(incorporated by reference in Applicant's Specification; pg 91 ln 13-14)[emphasis added]. This common knowledge has been utilized to develop a number of transgenic animals using salivary gland-specific expression constructs. For example,

> Therefore, this strain [SWR/J taster mice] provided the Prp transgenes used in the present study. The host mice were from strain FVB/NtacfBR (FVB), an inbred strain often used as transgenic hosts. *pg 40 lhc.*

and,

> Oocytes from the FVB non-taster mouse were microinjected with the fragments, and transgenic mice were generated according to standard procedures (Brinster et al., 1985). *pg 40 rhc.*

Harder et al., "Sucrose Octaacetate Avoidance In Nontaster Mice Is Not Enhanced By Two Type-A Prp Transgenes From Taster Mice" *Chem Senses* 25:39-45 (2000)[emphasis added]. The creation of transgenic PRP animals has been used to support basic genetic engineering experimentation. For example:

> Recently, we have taken a transgenic approach to locate the regulatory regions that are essential for tissue-specific and inducible expression of rat PRP gene ... The expression profiles of 18 independent transgenic lines harboring fusion constructs ... are analyzed (16). pg 27-37 lhc.

Lin et al., "Involvement Of Nuclear Orphan Receptor NGFI-B In Transcriptional Activation Of Salivary-Specific R15 Gene By cAMP", *J Biol Chem* 271:27673-27644 (1996)[emphasis added]. Others have proposed that collecting saliva from PRP and/or PSP transgenic mice and/or pigs have promise to support commercial ventures. For example:

> ... we produced transgenic mice that secrete phytase in their saliva. The transgenes used in these studies contain the E. coli appA gene[ ], which was recently shown to be effective in poultry[ ], regulated either by the inducible proline-rich protein (PRP) R15 promoter from the rat[ ] or the constitutive parotid secretory protein (PSP) promoter from the mouse[14]. *pg 429 lhc.*

and,

> Here we validate a method ... by providing monogastric animals with an exogenous gene for production of phytase in the saliva. ... The specific expression of R15/APPA and PSP/APPA transgenes contain all the elements required to achieve salivary-specific expression of the heterologous transgene. *pg 431 lhc.*

and,

> Our data and those of others[ ] also demonstrate that salivary glands can be used for efficient production of other heterologous proteins. Animals of both sexes start producing saliva early and do so throughout their life. Pigs, for example, can produce an average 15 L of saliva per day containing an average protein concentration of 4 mg/ml (60 g protein per day) ... In pursuit of this objective, we have recently produced transgenic pigs producing salivary phytase ... *pg 432 lhc.*

Golovan et al., "Transgenic Mice Expressing Bacterial Phytase As A Model For Phosphorus Pollution Control" *Nature Biotechnology*, 19:429-433 (2001)[emphasis added]. The Applicant has relied upon this common knowledge in the art such that one having ordinary skill in the art would understand that the written description was scientifically proper and correct.

Consequently, the Applicant refers to Mikkelsen et al. reporting a PSP transgenic mouse who teaches that:

> A PSP minigene, Lama, which can also be used as an expression vector for foreign coding sequences, was built from sequences derived from the PSPS gene ... *pg 2250 rhc.*

and,

> Heterologous cDNAs or genomic fragments can be inserted into the Lama construct in the proper reading frame. They are expected ... to result in hybrid proteins equipped with the same secretory signal peptide derived from Lama. Thus, the protein specified by the heterologous DNA should be directed to saliva. *pg 2251 lhc.*

and in summary,

> Here we report that a murine PSP minigene can be expressed in a correct tissue specific manner in the salivary glands of transgenic mice. A construct based on the PSP gene, Lama, containing 4.6 kb of 5' flanking genomic sequence, exon α, intron 1, parts of exons b and h, exon i and 0.5 kb 3' flanking genomic sequence is specifically expressed in two of the three major salivary glands, the sublingual and the parotid gland. Thus, the Lama construct is expressed in the same tissues as the endogenous PSP gene. *pg 2254 lhc.*

Mikkelsen et al., "Tissue-Specific Expression In The Salivary Glands Of Transgenic Mice" *Nucleic Acids Research* 20:2249-2255 (1992)(incorporated by reference in Applicant's Specification)[emphasis added].

In view of, Wagner et al., Lord S.T., Harder et al., Lin et al., Golovan et al., and Mikkelsen et al. the Applicants respectfully request the Examiner withdraw the rejection.

III. Claims 2-4, 14-15, 23, 25-26, and 29-40 Are Not Indefinite

The Examiner states that:

> Claims 2-4, 14-15, 23, 25-26, and 29-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Office Action, pg 13. The Applicant disagrees. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicant has amended Claims 1 and 20 to comprise " a genome comprising an exogenous nucleic acid encoding at least one transgenic polypeptide, said nucleic acid operably linked to a salivary-gland-specific cis-acting transcriptional control region" and Claim 29 to recite that the DNA sequences are "derived from a salivary gland secretory protein gene" and that the injected embryo may be selected from species selected from

"porcine, bovine, ovine, caprine, and equine". These amendments resulted in the concomitant cancellation of Claims 14, 30-31, and 36-40. The Examiner should also note that Claims 15, 25, and 32 were amended to improve clarity. These amendments are made not to acquiesce to the Examiner's argument but only to further the Applicant's business interests, better define one embodiment and expedite the prosecution of this application. The Examiner is reminded that with the cancellation of Claim 36-40, the pending construction objections are now moot.

The Applicant respectfully requests the Examiner to withdraw this rejection.

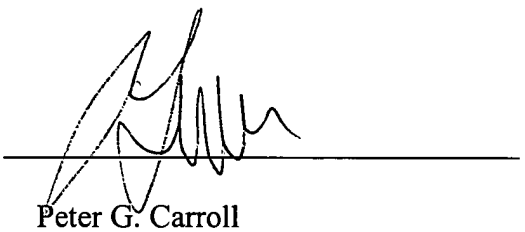
IV. The Specification Contains A Priority Statement

The Examiner properly notes that the Applicant's specification has priority to United States Provisional Application 60/357,641, filed February 20, 2002. *See Office Action pg. 2.* The Examiner is reminded that, as a Patent Cooperation Treaty application, this priority is noted on the front page of WO 03/069984 A2. Consequently, it is clear that the pending application was properly filed with the priority designation. Nevertheless, and at the Examiner's request, the Applicant provides above a priority statement for insertion as the first paragraph of the Applicant's specification.

CONCLUSION

The Applicant believes that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicant encourages the Examiner to call the undersigned collect at 617.984.0616.

Dated: May 8, 2006

By: 

Peter G. Carroll
Registration No. 32,837

MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, CA 94105
617.984.0616